Amendments to the Specification:

Please replace the "cross-reference to related applications" section with the following replacement section.

~~This application is a continuation in part of USSN 322,289, filed May 28, 1999, which is incorporated by reference in its entirety for all purposes.~~

This application is a continuation of U.S. Application No. 09/580,018, filed May 26, 2000. This application is also a continuation-in-part of U.S. Application No. 322,289, filed May 28, 1999, which is a continuation-in-part of U.S. Application No. 09/201,430, filed November 30, 1998, which claims the benefit under 35 U.S.C. 119(e) of U.S. Application No. 60/080,970, filed April 7, 1998 and U.S. Application 60/067,740, filed December 2, 1997, all of which are incorporated by reference in their entirety for all purposes.

Please replace the paragraph beginning on page 2, line 21 of the specification with the following replacement paragraph.

~~This application is related to Townsend and Townsend and Crew Attorney Docket 015270-004750PC, filed May 26, 2000, PCT/US98/25386, filed November 30, 1998, USSN 60/067,740, filed December 2, 1997, USSN 60/080,970, filed April 7, 1998, and USSN 09/201,430, filed November 30, 1998, each of which is incorporated by reference in its entirety for all purposes.~~

This application is related to International Application No. PCT/US00/14810 filed May 26, 2000, Publication No. WO 00/72880; and, International Application No. PCT/US98/25386, filed November 30, 1998, Publication No. WO 99/27944; both of which are incorporated by reference in their entirety for all purposes.

Please replace the paragraph beginning on page 7, line 14 of the specification with the following replacement paragraph.

Fig. 10: Lymphocyte Proliferation Assay on spleen cells from AN1792-treated (Fig. 10A)~~(upper panel)~~ or PBS-treated (Fig. 10B) ~~(lower panel)~~.

Please replace the paragraph on page 7, beginning on line 27 with the following replacement paragraph.

Figs. 15~~(A-E)~~A-E: Aβ levels in the cortex of 12-month old PDAPP mice treated with AN1792 or AN1528 in combination with different adjuvants. The Aβ level for individual mice in each treatment group, and the median, mean, and p values for each treatment group are shown.

Please add the following five new paragraphs after the paragraph beginning on page 7, line 27.

Fig. 15A: The values for mice in the PBS-treated control group and the untreated control group.

Fig. 15B: The values for mice in the AN1528/alum and AN1528/MPL-treatment groups.

Fig. 15C: The values for mice in the AN1528/QS21 and AN1792/Freund's adjuvant treatment groups.

Fig. 15D: The values for mice in the AN1792/Thimerosol and AN1792/alum treatment groups.

Fig. 15E: The values for mice in the AN1792/MPL and AN1792/QS21 treatment groups.

Please replace the paragraph beginning on page 7, line 32 with the following replacement paragraph:

Fig. 19: Epitope Map: Restricted N–terminal Response. Day 175 serum from cynomolgus monkeys was tested by ELISA against a series of 10–mer overlapping peptides (SEQ ID NOS:1-41) covering the complete AN1792 sequence. ~~The results for peptide VGSNKGAII (SEQ ID NO:32) are shown twice.~~ Animal number F10920M shows a representative N–terminal restricted response to the peptide DAEFRHDSGY (SEQ ID NO:9) which covers amino acids 1–10 of the AN1792 peptide which was used as immunizing antigen.

Please replace the paragraph beginning at page 8, line 5 with the following replacement paragraph:

Fig. 20: Epitope Map: Non–restricted N–terminal response. Day 175 serum from cynomolgus monkeys was tested by ELISA against a series of 10-mer overlapping peptides (SEQ ID NOS:1-41) covering the complete AN1792 sequence. ~~The results for peptide VGSNKGAII (SEQ ID NO:32) are shown twice.~~ Animal number F10975F shows a representative non–restricted N–terminal response. Reactivity is seen against the two peptides N–terminal and one peptide C-terminal to the peptide DAEFRHDSGY (SEQ ID NO:9) which covers amino acids 1–10 of the AN1792 peptide.

Please replace the paragraph beginning at page 16, line 16, with the following replacement paragraph:

In a further variation, an immunogenic peptide, such as a fragment of Aβ, can be presented by a virus or a bacteria as part of an immunogenic composition. A nucleic acid encoding the immunogenic peptide is incorporated into a genome or episome of the virus or bacteria. Optionally, the nucleic acid is incorporated in such a manner that the immunogenic peptide is expressed as a secreted protein or as a fusion protein with an outer surface protein of a virus or a transmembrane protein of a bacteria so that the peptide is displayed. Viruses or bacteria used in such methods should be nonpathogenic or attenuated. Suitable viruses include adenovirus, HSV, Venezuelan equine encephalitis virus and other alpha viruses, vesicular stomatitis virus, and other rhabdo viruses, vaccinia and fowl pox. Suitable bacteria include ~~Salmonella~~*Salmonella* and ~~Shigella~~*Shigella*. Fusion of an immunogenic peptide to HBsAg of HBV is particularly suitable. Therapeutic agents also include peptides and other compounds that do not necessarily have a significant amino acid sequence similarity with Aβ but nevertheless serve as mimetics of Aβ and induce a similar immune response. For example, any peptides and proteins forming β-pleated sheets can be screened for suitability. Anti-idiotypic antibodies against monoclonal antibodies to Aβ or other amyloidogenic peptides can also be used. Such anti-Id antibodies mimic the antigen and generate an immune response to it (*see Essential Immunology* (Roit ed., Blackwell Scientific Publications, Palo Alto, 6th ed.), p. 181). Agents other than Aβ peptides should induce an immunogenic response against one or more of the preferred segments of Aβ listed above (e.g., 1-10, 1-7, 1-3, and 3-7). Preferably, such agents induce an immunogenic response that is specifically directed to one of these segments without being directed to other segments of Aβ.

Please replace the paragraph beginning on page 46, line 19 with the following replacement paragraph:

The methods work by administering a reagent, such as antibody, that binds to Aβ in the patient~~to the patient~~, and then detecting the agent after it has bound. Preferred antibodies bind to Aβ deposits in a patient without binding to full length APP polypeptide. Antibodies binding to an epitope of Aβ within amino acids 1-10 are particularly preferred. In some methods, the antibody binds to an epitope within amino acids 7-10 of Aβ. Such antibodies typically bind without inducing a substantial clearing response. In other methods, the antibody binds to an epitope within amino acids 1-7 of Aβ. Such antibodies typically bind and induce a clearing response to Aβ. However, the clearing response can be avoided by using antibody fragments lacking a full length constant region, such as Fabs. In some methods, the same antibody can serve as both a treatment and diagnostic reagent. In general, antibodies binding to epitopes C-terminal of residue 10 ~~of Aβdo not~~of Aβ do not show as strong signal as antibodies binding to epitopes within residues 1-10, presumably because the C-terminal epitopes are inaccessible in amyloid deposits. Accordingly, such antibodies are less preferred.

Please replace the paragraph beginning at page 59, line 25, with the following replacement paragraph:

Spleens were removed from nine AN1792-immunized and 12 PBS-immunized 18-month old PDAPP mice 7 days after the ninth immunization. Splenocytes were isolated and cultured for 72 h in the presence of Aβ40, Aβ42, or Aβ40-1 (reverse order protein). The mitogen Con A served as a positive control. Optimum responses were obtained with >1.7 μM protein. Cells from all nine AN1792-treated animals proliferated in response to either Aβ1-40 or Aβ1-42 protein, with equal levels of incorporation for both proteins (Fig. 10A)~~(Fig. 10, Upper Panel)~~. There was no response to the Aβ40-1 reverse protein. Cells from control animals did not respond to any of the Aβ proteins (Fig. 10B)~~(Fig. 10, Lower Panel)~~.

Please replace the paragraph beginning at page 62, line 12, with the following replacement paragraph:

Preparation of the pBx6 protein: An expression plasmid encoding pBx6, a fusion protein consisting of the 100-amino acid bacteriophage MS-2 polymerase N-terminal leader sequence followed by amino acids 592-695 of APP (βAPP) was constructed as described by Oltersdorf et al., J. Biol. Chem. 265, 4492-4497 (1990). The plasmid was transfected into ~~E. coli~~*E. coli* and the protein was expressed after induction of the promoter. The bacteria were lysed in 8M urea and pBx6 was partially purified by preparative SDS PAGE. Fractions containing pBx6 were identified by Western blot using a rabbit anti-pBx6 polyclonal antibody, pooled, concentrated using an Amicon Centriprep tube and dialysed against PBS. The purity of the preparation, estimated by Coomassie Blue stained SDS PAGE, was approximately 5 to 10%.

Please replace the paragraph beginning on page 68, line 17 with the following replacement paragraph:

Groups of 7-9 month old PDAPP mice each are injected with 0.5 mg in PBS of polyclonal anti-Aβ or specific anti-Aβ monoclonals as shown below. The cell line designated RB44-10D5.19.21 producing the antibody 10D5 has the ATCC accession number PTA-5129, having been deposited on April 8, 2003. All antibody preparations are purified to have low endotoxin levels. Monoclonals can be prepared against a fragment by injecting the fragment or longer form of Aβ into a mouse, preparing hybridomas and screening the hybridomas for an antibody that specifically binds to a desired fragment of Aβ without binding to other nonoverlapping fragments of Aβ.

Please replace the paragraph beginning on page 76, line 17 with the following amended paragraph:

To prepare formulation doses with alum (Groups 1 and 5). Aβ peptide in PBS was added to Alhydrogel (two percent aqueous aluminum hydroxide gel, Sargeant, Inc., Clifton, NJ) to reach concentrations of 100 μg Aβ~~peptide per 1 mg of alum~~ peptide per 2 mg of alum. 10X PBS was added to a final dose volume of 200 ml in 1X PBS. The suspension was then gently mixed for approximately 4 hr at RT prior to injection.

Please replace the paragraph beginning at page 77, line 3, with the following amended paragraph:

To prepare formulation doses with Freund's Adjuvant (Group 4), 100 g of AN1792 in 200 μl PBS was emulsified 1:1 (vol:vol) with Complete Freund's Adjuvant (CFA) in a final volume of 400 μl for the first immunization. For subsequent immunizations, the antigen was similarly emulsified with Incomplete Freund's Adjuvant (IFA). For the formulations containing the adjuvants alum, MPL or QS21, 100 g per dose of AN1792 or AN1528 was combined with alum ~~(1 mg per dose)~~ (2 mg per dose) or MPL (50 g per dose) or QS21 (25 g per dose) in a final volume of 200 μl PBS and delivered by subcutaneous inoculation on the back between the shoulder blades. For the group receiving FA, 100 g of AN1792 was emulsified 1:1 (vol:vol) with Complete Freund's adjuvant (CFA) in a final volume of 400 μl and delivered intraperitoneally for the first immunization, followed by a boost of the same amount of immunogen in Incomplete Freund's adjuvant (IFA) for the subsequent five doses. For the group receiving AN1792 without adjuvant, 10 g AN1792 was combined with 5 g thimerosal in a final volume of 50 μl PBS and delivered subcutaneously. The ninth, control group received only 200 μl PBS delivered subcutaneously. Immunizations were given on a biweekly schedule for the first three doses, then on a monthly schedule thereafter on days 0, 16, 28, 56, 85 and 112. Animals were bled six to seven days following each immunization starting after the second dose for the measurement of antibody titers. Animals were euthanized approximately one week after the final dose. Outcomes were measured by ELISA assay of Aβ and APP levels in brain and by immunohistochemical evaluation of the presence of amyloid plaques in brain sections. In addition, Aβ-specific antibody titers, and Aβ-dependent proliferative and cytokine responses were determined.

Please replace the paragraph beginning at page 80, line 1, with the following amended paragraph:

The results of AN1792 or AN1592 treatment with various adjuvants, or thimerosal on cortical amyloid burden in 12-month old mice determined by ELISA are ~~shown in Fig. 15~~shown in Figs 15A-15E. In PBS control PDAPP mice the median level of total Aβ in the cortex at 12 months was 1,817 ng/g (Fig. 15A). Notably reduced levels of Aβ were observed in mice treated with AN1792 plus CFA/IFA (Fig 15C), AN1792 plus alum (Fig 15D), AN1792 plus MPL (Fig 15E) and QS21 plus AN1792 (Fig 15E). The reduction reached statistical significance ($p<0.05$) only for AN1792 plus CFA/IFA (Fig 15C). However, as shown in Examples I and III, the effects of immunization in reducing Aβ levels become substantially greater in 15 month and 18 month old mice. Thus, it is expected that at least the AN1792 plus alum, AN1792 plus MPL and AN1792 plus QS21 compositions will achieve statistical significance in treatment of older mice. By contrast, the AN1792 plus the preservative thimerosal (Fig 15D) showed a median level of Aβ about the same as that in the PBS treated mice. Similar results were obtained when cortical levels of Aβ42 were compared. The median level of A42 in PBS controls was 1624 ng/g. Notably reduced median levels of 403, 1149, 620 and 714 were observed in the mice treated with AN1792 plus CFA/IFA, AN1792 plus alum, AN1792 plus MPL and AN1792 plus QS21 respectively, with the reduction achieving statistical significance ($p=0.05$) for the AN1792 CFA/IFAβ treatment group. The median level in the AN1792 thimerosal treated mice was 1619 ng/g Aβ42.

Please replace the paragraph beginning on page 83, line 14 with the following replacement paragraph:

Sixty male and female, heterozygous PDAPP transgenic mice, 8.5 to 10.5 months of age were obtained from Charles River Laboratory. The mice were sorted into six groups to be treated with various antibodies directed to Aβ. Animals were distributed to match the gender, age, parentage and source of the animals within the groups as closely as possible. As shown in Table 10, the antibodies included four murine Aβ-specific monoclonal antibodies, 2H3 (directed to Aβ residues 1-12), 10D5 (directed to Aβ residues 1-16) (details of the deposit of 10D5 are discussed in Example VI, *supra*), 266 (directed to Aβ residues 13-28 and binds to monomeric but not to aggregated AN1792), 21F12 (directed to Aβ residues 33-42). A fifth group was treated with an Aβ-specific polyclonal antibody fraction (raised by immunization with aggregated AN1792). The negative control group received the diluent, PBS, alone without antibody.

Please replace the paragraph beginning on page 107, line 26 with the following replacement paragraph:

The brain homogenates were diluted 1:10 with ice cold Casein Diluent (0.25% casein, PBS, 0.05% sodium azide, 20 μg/ml aprotinin, 5 mM EDTA pH 8.0, 10 μg/ml leupeptin) and then centrifuged at 16,000 x g for 20 min at 4 C. The synthetic Aβ protein standards (1-42 amino acids) and the APP standards were prepared to include 0.5 M guanidine and 0.1% bovine serum albumin (BSA) in the final composition. The "total" Aβ sandwich ELISA utilizes monoclonal antibody (mAb) 266, specific for amino acids 13-28 of Aβ (Seubert, et al.), as the capture antibody, and biotinylated mAb 3D6, specific for amino acids 1-5 of Aβ (Johnson-Wood, et al), as the reporter antibody. The 3D6 mAb does not recognize secreted APP or full-length APP, but detects only Aβ species with an amino-terminal aspartic acid. The cell line producing the antibody 3D6 has the ATCC accession number PTA-5130, having been deposited on April 8, 2003. This assay has a lower limit of sensitivity of ~50 ng/ml (11 nM) and shows no cross-reactivity to the endogenous murine Aβ protein at concentrations up to 1 ng/ml (Johnson-Wood et al., *supra*).